PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 638	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/DK2004/000490	International filing date *(day/month/year)* 09.07.2004	Priority date *(day/month/year)* 24.07.2003
International Patent Classification (IPC) or national classification and IPC C07C225/22, C07C275/40, A61K31/136, A61P27/02, A61P29/00, A61P35/00		
Applicant LEO PHARMA A/S		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the International application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.05.2005	16.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Bueno Torres, M Telephone No. +49 89 2399-8290

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000490

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

1-213	as originally filed

   Claims, Numbers

2-48	as originally filed
1	received on 25.05.2005 with letter of 20.05.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 41-45

because:

☒ the said international application, or the said claims Nos. 41-45 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-48
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-48
Industrial applicability (IA)	Yes:	Claims	1-40, 46-48
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Re Item III.

Claims 41-45 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the **industrial applicability** of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV.

As stated by the applicant (see page 1) the core structure common to all the compounds of formula (I) according to claim 1 is already known in connection inhibitors of interleukin 1beta(IL-1beta) and tumour necrosis factor alpha (see D1-D9).

Moreover, these documents already disclosed compounds showing a 2-R_1 and 4-R_6 or 5-R_5 pattern of substitution of the ring A (see the references of the search report).

Therefore, there is not any structural feature **common to all the compounds of formula (I)** representing the structural contribution which differentiates **all** the present compounds from the compounds disclosed in D1-D9 already in connection with the same pharmacological activities.

Therefore, all the multiple structural combinations of the compounds of formula (I) according to claim 1 and specially the structural subgroups encompassed within the definitions of the **4 provisos** of claim 1 are not so linked as to form a common single inventive concept, as required by Rule 13(1)PCT.

Re Item V.

D1: WO 01/05744 A (OTTOSEN ERIK RYTTER ; LEO PHARM PROD LTD (DK); BJOERKLING FREDRIK (SE)) 25 January 2001 (2001-01-25)

D2: WO 01/05745 A (OTTOSEN ERIK RYTTER ; LEO PHARM PROD LTD (DK)) 25 January 2001 (2001-01-25)

D3: WO 01/05746 A (OTTOSEN ERIK RYTTER ; LEO PHARM PROD LTD (DK))

25 January 2001 (2001-01-25)

D4: WO 01/05749 A (DANNACHER HEINZ WILHELM ; OTTOSEN ERIK RYTTER (DK); LEO PHARM PROD LTD) 25 January 2001 (2001-01-25)

D5: WO 01/05751 A (OTTOSEN ERIK RYTTER ; LEO PHARM PROD LTD (DK)) 25 January 2001 (2001-01-25)

D6: WO 01/42189 A (OTTOSEN ERIK RYTTER ; LEO PHARM PROD LTD (DK)) 14 June 2001 (2001-06-14)

D7: WO 02/45752 A (DIDRIKSEN ERIK JOHANNES; GROTH LOTTE ; HEDEMAN HANNE (DK); AAES HELLE) 13 June 2002 (2002-06-13)

D8: WO 02/076447 A (NOVARTIS ERFIND VERWALT GMBH ; NOVARTIS AG (CH); REVESZ LASZLO (CH)) 3 October 2002 (2002-10-03)

D9: WO 98/32730 (OTTOSEN ERIK RYTTER ; LEO PHARM PROD LTD (DK); 30 July 1998 (1998-07-30)

2. Claim 1 of the present application appears to be novel vis-à-vis D1-D9, mainly on account of the 4 provisos in the definition of said claim (Art. 33(2) PCT.

3. Claim 1 of the present application has been worded with 4 provisos in order to establish novelty over D1-D9 which disclose compounds **already known in connection with qualitatively the same pharmacological activities as the present compounds**. However, the presence of said provisos will not render an obvious teaching as inventive.

The problem underlying the invention is therefore considered to be the provision of compounds with unexpected or improved properties over the ones of the compounds of D1-D9.

Compounds structurally close to the compounds of the present application, namely compounds showing a 2-R_1 and 4-R_6 or 5-R_5 pattern of substitution of the ring A (see the references of the search report) are already known in connection with qualitatively the same pharmacological activities as the present compounds.

The applicant has provided with his letter of 20.05.05 additional activity data of

structurally related compounds of D1, D2, D3, D4, D5, D6 and D9.

However, said additional comparative data and the comparative data given on Table 1 (see pages 46-47 of the present application) are not sufficient in order to demonstrate that a structural feature **common to all the compounds of formula (I)** representing the structural contribution which differentiates them from the compounds disclosed in D1-D9 is responsible for a non obvious technical effect (see also item IV).

Therefore, said data are not regarded as an adequate support in order to demonstrate the presence of an inventive step for all or substantially all the compounds encompassed within the definition of claim 1.

For the above reasons, the subject-matter of claims 1-48 is not considered to fulfil the requirements of Art. 33(3)PCT.